DRUG DISPOSITION AND PHARMACOKINETICS

Key Words: CYP2D6, pharmacogenetics, personalized medicine, alcohol-induced psychotic disorders, haloperidol

Association of *CYP2D6*4* Polymorphism with the Steady-State Concentration of Haloperidol in Patients with Alcohol-Induced Psychotic Disorders

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ABSTRACT ~ ***Background:*** *CYP2D6 subfamily isoenzymes play an important role in the biotransformation of haloperidol, and their activity may influence the efficacy and safety of haloperidol. The use of haloperidol is often associated with the occurrence of adverse drug reactions (ADRs), such as dyskinesia, acute dystonia, and orthostatic hypotension. Previous studies have demonstrated the relationship between the CYP2D6*4 genetic polymorphism and CYP2D6 activity, as well as haloperidol efficacy and safety rates.* ***Purpose:*** *To evaluate the association of CYP2D6*4 genetic polymorphism with the steady-state concentration of haloperidol in patients with acute alcohol-induced psychotic disorders (AIPDs).* ***Material and methods:*** *The study involved 100 male patients with AIPD (average age 41.4 ± 14.4 years) who received haloperidol by injections in a dose of 5–10 mg/day. The efficacy profile was assessed using a validated psychometric PANSS scale (Positive and*

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Negative Syndrome Scale). Therapy safety was assessed using the internationally validated UKU (Side-Effect Rating Scale) and SAS (Simpson-Angus Scale for Extrapyramidal Symptoms) scales. Genotyping was performed with the real-time polymerase chain reaction. ***Results:*** *We revealed the statistically significant results in terms of therapy safety evaluation (dynamics of the UKU scores: (GG) 8.00 [7.00; 10.00], (GA) 15.0 [9.25; 18.0], $p < 0.001$; dynamics of the SAS scores: (GG) 11.0 [9.0; 14.0], (GA) 14.50 [12.0; 18.0], $p < 0.001$. Pharmacokinetic study showed a statistically significant difference across the groups with different genotypes: (GG) 3.13 [2.32; 3.95], (GA) 3.89 [2.92; 5.26], $p = 0.010$.* ***Conclusion:*** *It can be concluded that patients with the GA genotype have a higher risk of ADRs compared to patients who carry the GG genotype. It was shown that CYP2D6*4 genetic polymorphism has a statistically significant effect on the steady-state concentration of haloperidol.* Psychopharmacology Bulletin. *2022;52(4):52–60.*

Introduction

Acute alcoholic hallucinoses, or alcohol-induced psychotic disorders (AIPDs) rank second in prevalence rates among alcohol-related psychotic disorders requiring emergency medical care.[1] According to a study by Egorov, incidence rate ratio of delirium tremens to alcoholic hallucinosis is 2.27:1 for the group of patients with a family history of alcohol use disorders (AUDs) and 4.67:1 for the group with no history of AUDs.[2] Available data indicate that the incidence of AIPD ranges from 5.6% to 22.8%.[3,4] Prevalence rates of different AIPD variants vary: in a study by Nemkova, it was revealed that the most frequent AIPD variant is abortive (51%), followed by the typical AIPD (31%); AIPD with the elements of syndrome of the psychic automatism (5%); AIPD with predominant visual hallucinations (4%); AIPD with predominant delusional disorders (3%); and AIPD with predominant depression (1%).[5]

Treatment of patients with acute alcoholic hallucinosis requires obligatory prescription of neuroleptics with pronounced antipsychotic effect, for instance, haloperidol.[6,7] Haloperidol belongs to the group of typical antipsychotic drugs and possesses an antidopaminergic effect through the pronounced actions in the dopamine D2 receptors. Haloperidol blocks the D2 receptors and therefore relieves positive psychopathological symptoms.[8]

It is suggested that antidopaminergic activity in the dorsolateral striatum may contribute to extrapyramidal adverse drug reactions (ADRs) associated with the action of typical antipsychotic drugs, including haloperidol.[9] Extra-pyramidal ADRs such as acute dystonia, akathisia, malignant neuroleptic syndrome, parkinsonism, and tardive dyskinesia are common when using haloperidol. Haloperidol also shows noradrenergic, cholinergic, and histaminergic blocking actions which are associated with the occurrence of various ADRs.[10]

Haloperidol undergoes biotransformation in the liver with the participation of cytochrome P450 family enzymes.[11,12] The main isoenzyme involved in haloperidol metabolism is CYP2D6 which is encoded by the gene of the same name.[13] The *CYP2D6* gene is located on chromosome 22 (*22q13.1*) and is translated into the CYP2D6 protein that is localized in the endoplasmic reticulum and expressed in the liver, brain, intestinal tissue and lymphoid cells.[14] It is important to note that CYP2D6 accounts for only 2–4% of all cytochromes in the liver;[15] it is the main drug-metabolizing enzyme involved in the metabolism of approximately 20% of commonly used medications.[16]

One of the most studied *CYP2D6* genetic polymorphisms is *CYP2D6*4* (*rs3892097*), which leads to CYP2D6 isoenzyme deactivation, resulting in the reduced metabolism of substrate drugs,[17] including haloperidol.[18]

Categorization of CYP2D6 metabolizer status is based on the evaluation of the enzymatic activity, which allows to determine the type of metabolizer on the basis of genetic data.[19] Thus, there are five categories of metabolizers: poor metabolizers (PM), intermediate metabolizers (IM), normal, or extensive metabolizers (EM), rapid metabolizers (RM), and ultrarapid metabolizers (UM).[20] Current pharmacogenetic guidelines use these categories to provide the clinicians with recommendations for specific drugs to adjust doses or switch medications that are expected to cause ADRs in patients with a particular CYP2D6 metabolizer status.[21]

The results of the studies conducted to date show that the risk of ADRs during the administration of antipsychotic drugs, including haloperidol, depends on both clinical factors and individual characteristics of pharmacodynamics and pharmacokinetics of drugs.[11]

The study aimed to evaluate the association of *CYP2D6*4* genetic polymorphism with the steady-state concentration of haloperidol in patients with AIPDs.

Material and Methods

Present study involved 100 male patients (average age—41.40 ± 14.40 years) who were hospitalized to Moscow Research and Practical Centre on Addictions due to the diagnosis of AIPD with predominant hallucinations (F10.52, according to ICD-10). Haloperidol in injections at a dose of 5–10 mg/day was prescribed to this cohort of patients for 5 days for the treatment of acute hallucinatory symptoms. Haloperidol was administered upon the admission of a patient to the emergency department. In addition to haloperidol, all patients received minimal standard therapy for 5 days, which included infusions and ion-containing solutions, as well as vitamins (see Table 1). Prescriptions

TABLE 1

Minimal Standard Therapy

MEDICATIONS	AVERAGE DAILY DOSE
Sodium chloride solution 0.9% + potassium chloride 10% + magnesium sulfate 25%	800 mL
Thiamine hydrochloride solution 5%	100 mg
Pyridoxine hydrochloride solution 5%	100 mg

were made in accordance with the national clinical guidelines for the therapy of AIPD.

The inclusion criterion was the diagnosis of AIPD with predominant hallucinations (F10.52, according to ICD-10). Exclusion criteria were creatinine clearance values <50 mL/min, creatinine concentration in plasma >1.5 mg/dL (133 mmol/L), bodyweight less than 60 kg or greater than 100 kg, age of 75 years or more, presence of any other psychotropic medications in the treatment regimen, presence of chronic psychotic disorders, and presence of any contraindications for haloperidol use.

Each patient signed an informed consent to voluntarily participate in the study. The study was approved by the local ethical committee of the Russian Medical Academy of Continuing Professional Education of the Ministry of Health of Russia (Protocol No. 14 of October 27, 2020).

For genotyping, venous blood samples were collected into VACUETTE® (Greiner Bio-One, Austria) vacuum tubes on day 6 of haloperidol therapy. The single nucleotide polymorphism (SNP) *rs3892097* (*CYP2D6*4*) was analyzed by real-time PCR using "Dtlite" DNA amplifiers (DNA Technology, Moscow, Russia) on a CFX96 Touch Real-Time System with CFX Manager software (Bio-Rad Laboratories Inc., Hercules, CA, USA) and the "SNP-screen" sets (Syntol, Moscow, Russia). In every set, two allele-specific hybridizations were used, which allowed simultaneous determination of both alleles of the respective SNP using two fluorescence channels.

To assess haloperidol efficacy, the Positive and Negative Syndrome Scale (PANSS) was used.[22] The safety profile was evaluated using the UKU[23] and SAS[24] scales. Patients were examined on days 1 and 6 of haloperidol therapy.

Statistical analysis was performed in Statsoft Statistica v. 10.0 (Dell Statistica, Tulsa, OK, USA). The normality of sample distribution was evaluated using the Shapiro-Wilk test and was taken into account for selecting parametric or non-parametric tests. The differences were considered statistically significant at $p < 0.05$ (power above 80%). Two samples of continuous independent data were compared using the

Mann-Whitney U-tests with further correction of the obtained p-value using the Benjamin-Hochberg test, due to the multiple comparison procedure. Research data are presented in the form of the median and interquartile range (Me [Q1; Q3]).

Results

The *CYP2D6* genotyping performed on 100 subjects revealed the following results. In total, 70 out of 100 patients did not carry the *CYP2D6*4* allele, whereas 30 patients were heterozygous for the respective variant.

Further study included a comparison of the therapy efficacy and safety rates in major allele carriers (main group) and minor allele carriers (comparison group).

The results of data analysis performed for psychometric assessments (PANSS) and side-effect rating scales (UKU and SAS) on days 1 and 6 in patients who received haloperidol are presented in Table 2.

Then we compared the dynamics of changes in positive PANSS scale scores in patients with different genotypes (Figure 1). Statistical analysis of the clinical efficacy profile data obtained for the patients with different *CYP2D6* genotypes revealed no statistically significant differences: (*GG*) −13.00 [−16.00; −11.00], (*GA*) −15.00 [−16.75; −13.00], p = 0.078.

Table 3 shows the dynamics of changes in SAS and UKU scale scores in patients carrying different genotypes. Statistical analysis of haloperidol safety profile data obtained using the SAS and UKU scale scores in patients with different genotypes showed statistically significant differences.

TABLE 2

Data from the Psychometric Assessments and Side-Effect Rating Scales in Patients who Received Haloperidol, on Days 1 and 6 of the Study

SCALE	*GG* (N = 70)	*GA* (N = 30)	P*
Day 1			
PANSS	14.50 [13.00; 18.00]	16.00 [15.00; 18.00]	0.017
SAS	0 [0; 0]	0 [0; 0]	> 0.999
UKU	0 [0; 0]	0 [0; 0]	> 0.999
Day 6			
PANSS	1.00 [1.00; 2.00]	2.00 [1.00; 2.75]	0.006
SAS	11.00 [9.00; 14.00]	14.50 [12.00; 18.00]	< 0.001
UKU	8.00 [7.00; 10.00]	15.00 [9.25; 18.00]	< 0.001

Note: p* – p-value obtained in Benjamini–Hochberg multiple testing correction (based on the results of Mann–Whitney U test).

FIGURE 1

Effect of *CYP2D6*4* Genetic Polymorphism on Haloperidol Steady-State Concentration Levels

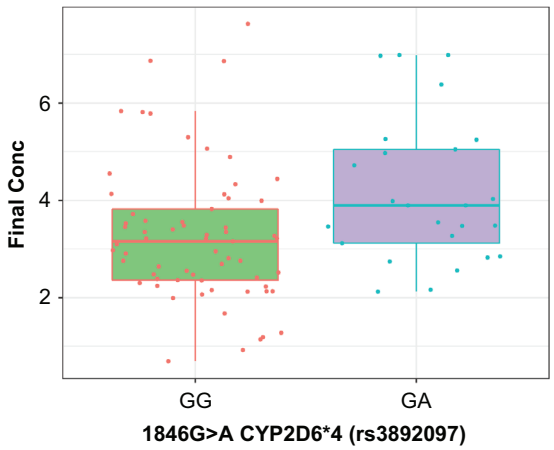

Table 4 shows the results of the pharmacokinetic study in patients with *GG* and *GA* genotypes.

The *CYP2D6*4* genetic polymorphism has been shown to have a statistically significant effect on the equilibrium concentration of haloperidol when administered to patients with AIPD (Figure 1).

Therefore, the study revealed no statistically significant differences in the efficacy of haloperidol therapy in patients with acute AIPDs carrying different *CYP2D6*4* genotypes. Meanwhile, a statistically significant difference in safety profile (as assessed by the UKU and SAS scales) was found. The dynamics were more obvious in the group of patients with the *GA* genotype compared with the carriers of the *GG* genotype. There was a statistically significant difference between the carriers of the *GG* and *GA* genotypes in haloperidol steady-state concentration levels, confirming the impact of the *CYP2D6*4* genetic polymorphism on haloperidol concentrations in patients with AIPD.

The results of the study will enable clinicians to optimise the dosing regimen of haloperidol in patients with acute AIPD to reduce the risk of dose-dependent ADRs.

TABLE 3

Changes in SAS and UKU Scores From Day 1 to Day 6 in Patients with Different Genotypes

SCALE	*GG* (N = 70)	*GA* (N = 30)	P
SAS	11.00 [9.00; 14.00].	14.50 [12.00; 18.00].	$p < 0.001$
UKU	8.00 [7.00; 10.00].	8.00 [7.00; 10.00]	$p < 0.001$

TABLE 4

Haloperidol Steady-State Concentration Values in Patients with Different Genotypes

GG	*GA*	P
3.13 [2.32; 3.95]	3.89 [2.92; 5.26]	0.010

Discussion

Our findings are consistent with the results of our previous study that focused on pharmacogenetic aspects only.[25] The results of the present study suggest that *CYP2D6*4* genotype may be a potentially important predictor of haloperidol efficacy and safety in patients with acute AIPD.

Haloperidol starting dose should be decreased by 25% in carriers of the *GA* genotype, whereas homozygous *GG* carriers should be prescribed haloperidol at a standard therapeutic dose. Current DPWG guideline on haloperidol pharmacogenetics recommend a 50% reduction of the starting dose for mutant homozygotes.[26] In our study, a worsening of the safety profile in heterozygous carriers was observed; therefore, an adjustment of the starting dose of haloperidol is needed. However, it is likely that dose correction should be not as pronounced as in the existing recommendations for homozygous patients.

This study has several important limitations: all patients were males; only one genetic polymorphism was included in the study; there were no homozygous carriers of the minor allele revealed.

A strength of the study is that patients had no mental or acute somatic comorbidities and received haloperidol monotherapy, which allows eliminating the effect of other medications on the efficacy of treatment.

Conclusion

Thus, in a study on a group of 100 patients with acute AIPD, an association between the *CYP2D6*4* polymorphism and the safety profile of haloperidol was demonstrated. A statistically significant difference between the carriers of the *GG* and *GA* genotypes was revealed in haloperidol steady-state concentration levels, confirming the impact of the *CYP2D6*4* genetic polymorphism on haloperidol concentrations in patients with AIPD. ✤

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